Review Article

ENAMEL TISSUE ENGINEERING: FROM MOLECULAR MECHANISMS TO REGENERATIVE DENTISTRY

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ABSTRACT

Dental enamel, the hardest tissue in the human body, plays a critical protective role in maintaining tooth integrity and function. However, its inability to self-repair following damage or disease represents a significant clinical challenge in restorative dentistry. This comprehensive literature review examines current and emerging techniques for enamel regeneration, restoration, and remineralization, synthesizing evidence from biochemical, cellular, and tissue engineering approaches. The review encompasses multiple major regeneration strategies: remineralization agents including fluoride therapy; biomimetic mineralization approaches utilizing calcium phosphate technologies and self-assembled peptides; rotary evaporation methods for controlled crystal formation; laser-assisted mineralization; in situ remineralization mimicking amelogenin functions; electrically accelerated remineralization; gene therapy utilizing ameloblast-like cells and induced pluripotent stem cells; and scaffold-based strategies for tissue engineering. Contemporary biomimetic materials have demonstrated superior remineralization potential compared to traditional fluoride-based approaches. Cell-based regeneration utilizing dental epithelial stem cells and iPSCs shows promise for creating enamel with properties approaching natural tissue. However, significant challenges persist in replicating enamel's complex hierarchical structure and achieving adequate mechanical properties. The field requires continued research to optimize regeneration parameters and develop scalable clinical protocols for routine clinical implementation.

Key words: Enamel regeneration, Enamel remineralization, Ameloblasts, Amelogenesis, Tissue engineering.

Introduction

Dental enamel, the outermost layer of the tooth's crown, represents the hardest tissue in the human body [1]. It serves a critical function by forming a barrier against temperature fluctuations, masticatory forces, and the acidic environment caused by food and bacteria [2]. Mature enamel is composed of 1% organic material, 3% water, and 95% inorganic material, primarily hydroxyapatite (HAp) crystals [3]. From the nanoscale to the microscale, its hierarchical structure is evident [4]. HAp crystals (Ca10 (PO4x)6 (OH)2) grow along the C-axis of the crystal and have a hexagonal configuration at the nanoscale [5]. There are other trace minerals, such as fluoride, zinc, magnesium, and sodium, which fluctuate in concentration according to mineral exposure and enamel thickness [1, 3]. Densely packed HAp crystals on the microscale form units known as enamel rods or prisms [4]. Further, proteins, lipids, and disordered crystals make up the inter-rods or inter-prismatic regions that divide these rods. The spaces between rods are softer than the rods themselves, although they are more resistant to acid degradation [1, 6]. The size of these prisms and inter-prism regions is affected by enamel thickness, as the outer layers have larger inter-prism areas and smaller prisms [6, 7]. Therefore, enamel has remarkable anisotropic mechanical capabilities attributed to the hierarchical structure and chemical makeup [8].

Histologically, ameloblasts, the cells that create enamel, go through several stages in the process of amelogenesis, a process that is regulated by molecular pathways. Amelogenesis goes through four stages: pre-secretory, secretory, transitional, and maturation stages [2, 9]. Prism layout and inter-prism spaces are controlled by ameloblasts, which originate from the inner enamel epithelium and provide an organic matrix [10]. During the presecretory phase, pre-ameloblasts develop from undifferentiated inner enamel organ cells and secrete proteins onto the pre-dentin. In contrast, mesenchyme-derived odontoblasts secrete pre-dentin at the future dentino-enamel junction (DEJ). The basal lamina will later be broken by the pre-ameloblasts. Consequently, future ameloblasts and odontoblasts can come into physical touch, initiating the creation of enamel and dentin through epithelial-mesenchymal signaling. The initial enamel is prismatic with random crystallite orientation, and crystallite production in the enamel matrix follows [9, 10].

Ameloblasts lengthen and create Tomes' process, which determines the prismatic pattern of enamel, during the secretory phase [10, 11]. Around 30% of the enamel is mineralized at this point, and the thickness of the enamel rises [12]. The Tomes' process vanishes and matrix protein release declines during the transition phase [2, 12]. Proteinases break down the enamel matrix during the maturation phase, allowing crystals to grow thicker and wider and filling in the gaps left by the matrix proteins [13]. In order to adapt to internal and external pH levels and promote ion transport, ameloblasts alternate between ruffle-ended and smooth-ended morphologies [14]. By removing

matrix proteins and enlarging enamel crystals, this stage completes enamel mineralization [14, 15]. While dentin and pulp can regenerate through dental pulp cells [16], ameloblasts undergo apoptosis after maturation, which prevents enamel from self-repairing following tooth eruption [2].

Over the years, various restorative materials like amalgam, resin composites, and ceramics have been employed in traditional enamel restoration methods. However, the ability to restore function and structure is constrained by the differences in physical, mechanical, and visual properties between these materials and natural enamel. Despite the keen interest in this area, creating alternative treatment methods to repair or regenerate enamel is challenging, attributed to the difficulty in replicating the native enamel characteristics. Therefore, the aim of this study is to examine the modern regenerative techniques of enamel. It further highlights the latest techniques employed for enamel restoration and remineralization.

Remineralization agents and fluoride therapy

Fluoride therapy has traditionally been used for enamel remineralization and dental cavity prevention [17, 18]. Although salivary fluoride is an intrinsic remineralization solution, its quantity remains very low [19]. When fluoride is available, fluoride ions (F-) replace hydroxyl groups (OH-) in the crystal lattice to form fluorapatite, which is less soluble and more demineralization resistant under acidic conditions than hydroxyapatite [20, 21]. As a result, fluoride in the form of fluorapatite reduces the breakdown of enamel by inhibiting the loss of phosphate and calcium ions [20]. However, the potential risk of fluorosis and excessive fluoride concentrations may be associated with adverse effects [20, 22]. Furthermore, each unit of fluorohydroxyapatite requires a specific number of ions of fluoride, calcium, and phosphate. Hence, the lack of these ions represents a limitation for the use of fluoride therapy in enamel remineralization [23, 24].

Another source of fluoride is ingestion through sources,such as lactation [25], respiration, and food, including milk, salt, and nutritional supplements of fluoride in milk, tablets, and drops [25]. In contrast to topical fluoride application, which has a post-eruptive enamel effect, ingestible fluoride may have a post-eruptive effect associated with dental fluorosis, if excessive amounts of fluoride are consumed during tooth development [26]. Providing calcium and phosphate minerals can increase remineralization; however, fluoride ions have a tendency to form insoluble calcium fluoride (CaF2) upon reaction with calcium ions, which depletes bioavailable fluoride ions [23]. Therefore, dental products do not combine calcium phosphate ions with fluoride ions [27]. An example is using dentifrices with two compartments to separate sodium fluoride (NaF) and dicalcium phosphate dihydrate. This eventually increases anticaries efficacy and fluoride delivery [23, 27].

Biomimetic mineralization and calcium phosphate technologies

Two calcium phosphate technologies have been developed to promote remineralization of enamel subsurface lesions. These technologies include casein phosphopeptide-stabilized amorphous calcium phosphate (CPP–ACP) and functionalized tricalcium phosphate (fTCP) [23]. However, the use of fluoride and calcium phosphate nanocrystals is protective only to the outermost 30 µm of enamel [28]. Furthermore, the mechanical and structural properties of the resulting HAp do not match those of natural enamel. A simple chemical technique demonstrated the potential to regenerate enamel directly under conditions close to physiological (37°C, 1 atm, pH 6.0). This method involved a combination of a solution of calcium phosphate with the chelating agent N-(2-hydroxyethyl) ethylene-diamine-N, N'', N'-triacetic acid (HEDTA), and finally adding a KF solution. This delayed nucleation and promoted the formation of larger crystals of more than 10 µm in length [28, 29]. When fluoride ions are introduced into the solution and integrated into the HAp lattice, hexagonal crystals of fluorapatite are formed. Several therapeutic limitations are encountered. A device is necessary to separate the mineralization solution from the oral environment, as the process spans several days. Moreover, the clinical safety of the chelating agent HEDTA is not confirmed. Furthermore, this technique is not capable of reconstructing the inter-prism sections [29]. The FDA-approved product silver diamine fluoride (SDF) is used to treat dental cavities. This solution can be applied to the caries-free areas to prevent decay. It is also effective in treating dental hypersensitivity, halting decay in primary teeth, preventing pit and fissure caries in erupting permanent teeth, sterilizing infected root canals, and preventing root caries in the geriatric population [30, 31]. Additionally, it prevents the dentin matrix from degrading and the dentin tissue from demineralizing. Furthermore, the SDF's antibacterial properties stop cariogenic biofilms from growing. One disadvantage of this approach is that carious lesions become discolored and black following SDF therapy, which may not satisfy patients. Calcium phosphate ion clusters and HAp have recently been used to create a biomimetic regenerative solution that, when applied to caries, can induce crystalline-amorphous mineralization and epitaxial crystal growth [32]. This solution is structurally similar to the original enamel and has the potential to restore enamel up to 2.7 µm thick [33].

Structures known as self-assembled peptides can be produced using a bottom-up approach due to various bonds and π–π stacking forces between small molecules, mostly peptide amphiphiles (PA) [34, 35]. These molecules consist of a hydrophilic head group with a peptide group attached to a hydrophobic tail group of a dialkyl chain. In aqueous environments, PA can spontaneously form nanostructures, and variations in pH, concentration, or divalent ion concentration can trigger the self-assembly process [36]. Chemical and physical properties influence the shape of

nanostructures made from self-assembling peptides. Because self-assembling peptides form fibrous structures with a high aspect ratio and have well-defined surface functional groups that periodically repeat in the structure and aid in mineral nucleation, their use in enamel regeneration is beneficial [37]. Additionally, these peptides are injectable and undergo in situ gelation, making them suitable as filling materials for irregularly shaped cavities. However, the self-assembling peptides may undergo proteolytic breakdown, limiting their therapeutic uses and reducing their efficacy on dental surfaces [38].

Advanced physical and chemical regeneration techniques

Rotary evaporation and controlled crystal growth

Rotary evaporation is a straightforward method that is effective in organizing crystal formation and regenerating dental structures, including enamel, dentin, titanium sheets, and polyethylene sheets [39, 40]. It produces organized structures with a controlled thickness quickly. This method involves growing HAp crystals under rotational evaporation in a remineralizing solution that contains calcium, phosphate, and fluoride minerals [40]. Silk fibroin can be used to modulate crystal formation due to structural similarity to amelogenin. It was found that the regenerated enamel-like crystals possess microstructure and mechanical properties that are equivalent to those of natural enamel [41].

Laser-assisted mineralization

Lasers are widely used in dentistry to whiten teeth and cut soft tissues. They are appropriate for enamel restoration applications because of their photothermal effects, which warm the surrounding area and transform the reaction environment into a hydrothermal oven, aiding in crystal development [42, 43]. By controlling the formation of HAp crystals in the areas and speeding up the mineralization of dental enamel, lasers can stop dental calculus from forming. Nevertheless, the diode laser source has the potential to damage the nerve cells in this layer by overheating the pulp [44, 45]. Consequently, additional research is required to confirm the efficacy of switching the laser source. Additionally, the tooth enamel is remineralized using femtosecond pulsed lasers (fs) by sintering specific material placed on damaged enamel. Like a thermal antenna, Fe2O3 NPs could absorb laser photons, scatter the heat nearby to fluorapatite crystals, and cause compression into a thick layer adherent to the native enamel [42, 44].

Electric field-guided biomimetic mineralization

Electrically-Induced Enamel Regeneration represents a groundbreaking clinical technique for quickly and effectively remineralizing dental cavities without the need for drilling or filling. This approach is applicable for repairing the entire depth of early-stage or moderate cavities through a painless procedure that eliminates the need for injections, drills, or restorative materials [46]. Moreover, this method conserves the healthy portion of the tooth during treatment, helping to maintain tooth integrity, and it can also be used for teeth whitening. The procedure involves placing a small handpiece on the decayed tooth surface and consists of two steps: initially, a remineralizing agent in paste or liquid form is applied to the cavities, followed by a brief application of an electric field to speed up the movement of mineral agents to the affected area [47].

Electrodeposition, or electrochemical deposition, is a straightforward and cost-effective technique used to apply a uniform layer onto substrates by means of an electrical field. This process is divided into two primary types: electrolytic deposition (ELD) and electrophoretic deposition (EPD). In ELD, metal ions undergo electrochemical reduction, or colloidal particles are formed through cathodic reactions, and these are then transported to the electrode to create a layer [48]. Conversely, in EPD, charged particles in a liquid suspension are directed towards the electrode. ELD typically results in thinner coatings compared to EPD. The ELD method has demonstrated the capability to simultaneously precipitate self-assembled amelogenin proteins and calcium phosphate (CaP) under physiological conditions, thereby enhancing crystal growth and improving the mechanical properties of enamel-like composite coatings. A notable benefit of this method is its ability to coat calcium phosphate or hydroxyapatite (HAp) onto substrates with porous or irregular surfaces at relatively low temperatures while allowing for controlled crystallinity [48-50]. Additionally, the gradual rise in local pH near the cathode can trigger the self-assembly of amelogenin proteins, as well as the supersaturation of CaP and crystal nucleation on the cathode. However, the high electric field conditions required in this process limit its potential for clinical application [48, 51].

In situ remineralization and amelogenin-based approaches

Enamel remineralization and regeneration can be achieved by imitating the capabilities of the organic matrix. Initially, native enamel apatite forms within a gel-like environment that contains various proteins, such as amelogenin. As the enamel matures, these organic molecules are largely broken down or removed [49]. Proteins within the organic matrix provide the structural skeleton for supporting crystal formation and growth during enamel development. The gel-like organic materials' physicochemical properties more accurately replicate the native enamel matrix compared to aqueous solution-based systems, thereby controlling crystal growth [52]. On the other hand, the extracellular matrix of proteins and proteases is crucial for enamel mineralization. Enamelin, ameloblastin, amelotin, and amelogenin constitute the primary enamel matrix proteins (EMPs) produced by ameloblasts, with the latter being the most vital in the process of enamel mineralization [53, 54]. Amelogenin influences mineralization by managing the crystallization of calcium and phosphate into well-formed crystals within prisms, including orientation, size, and length. Further, recombinant full-length amelogenin (rP172) was shown to promote under physiological conditions the

construction of organized needle-like fluoridated HAp crystals in a dose-dependent manner. Adding fluoride to amelogenin is also crucial for crystal remineralization and packing density [53, 55, 56]. Although in situ enamel remineralization is beneficial for early caries lesions, the difficulty and high cost of expressing and purifying amelogenin contribute to the limited clinical applications [53, 57].

Cell-based regeneration and stem cell therapy

Dental epithelial cell sources

Ameloblasts are responsible for forming natural enamel during tooth development, making cell-based enamel regeneration promising as it can mimic the natural process of enamel formation and create enamel with properties similar to native tissue. There are several dental cell sources available for enamel regeneration, which can be used to restore tooth enamel.

Primary enamel organ epithelial (EOE) cells are found in the enamel organ epithelium of an unerupted tooth and resemble ameloblasts, making them a potential source for generating new enamel. The initial epithelial-like cells in the tooth bud express amelogenin and can be found in either polygonal or stellate shapes. However, maintaining the primary characteristics of EOE cells during long-term in vitro cultivation is quite difficult [58, 59]. Culturing these cells poses two significant challenges: firstly, their growth is hindered when dental mesenchymal cells contaminate them, and secondly, they undergo terminal differentiation after several passages. Additionally, once a tooth erupts, these cells become inaccessible, necessitating alternative cell sources for adults without unerupted teeth [58, 60].

The epithelial cell rests of Malassez (ERM) are epithelial cells that exhibit stem cell-like properties and originate from Hertwig's epithelial root sheath (HERS). It remains in PDL throughout adulthood in order to maintain tissue homeostasis. It is thought to be the only dental-origin epithelial cells in adult teeth and is involved in the formation of tooth roots. These cells have the capacity to develop into ameloblasts and can be derived from either ERM in the root surface following dental extraction or from HERS in the open root apex [61, 62]. Adult human epithelial stem cells, which may be retrieved from extracted third molars, can be used as readily accessible autologous epithelial stem cells [63, 64].

Keratinocytes Human keratinocytes can be extracted from the skin's epidermis and utilized as a source of non-dental epithelial cells to form dental enamel. These cells are readily available and rapidly proliferate in cell culture. Fibroblast growth factor 8 (FGF8) and mouse embryonic dental mesenchyme have been shown to induce human keratinocyte cell sheets to differentiate into enamel-producing ameloblasts. However, these cells cannot be used as an ideal cell source for the development of bioengineered teeth in the future due to their relatively low induction rate of ameloblast differentiation. It has been observed that low temperature culture or FGF8 with Sonic Hedgehog protein (SHH) treatment greatly accelerates the rate of ameloblastic differentiation in human keratinocyte stem cells [65-68].

Ameloblast-like cell lines

Ameloblast-like cell lines are developed by implementing viral oncogenes into cells derived from dental tissues, enabling them to proliferate indefinitely and exhibit a gene expression profile akin to ameloblasts [69, 70]. These cell lines facilitate research into the molecular and cellular processes involved in amelogenesis and enamel regeneration without relying on animals for cell isolation. LS8, a cell line derived from mice, serves as a model for the secretory phase of amelogenesis due to its high expression of amelogenin, ameloblastin, enamelin, and Mmp20, although it cannot form calcified nodules [71, 72]. ALC, another mouse-derived cell line, simulates the maturation of ameloblasts and expresses amelogenin, odontogenic ameloblast-associated protein (Odam), Klk4, and amelogenin [73, 74]. This cell line also exhibits pronounced activity of alkaline phosphatase, forming calcified nodes. HAT-7 is a dental epithelial cell line retrieved from the rat incisors apical bud. This cell line has been shown through immunocytochemical studies to exhibit ameloblast characteristics, including the expression of amelogenin and ameloblastin, which are considered secretory phase markers. Further, maturation-stage markers are expressed, such as Klk4 and amelotin [75, 76]. Rat incisors are also the source of SF2, another dental epithelial cell line, which is useful for studying epithelial cell fate, matrix adhesion, and interactions with dental mesenchymal stem cells [77]. Lately, scientists created two immortalized epithelial cell lines from mouse EOE. EOE-2M and EOE-3M cell lines retain their proliferative ability and express amelogenin, ameloblastin, KLK4, and MMP20, making them suitable for studying the secretory and maturation stages [78, 79]. Unfortunately, mouse and rat cell lines are not applicable for human enamel repair, offering limited value for examining human enamel repair and regeneration.

Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) can be derived from various dental stem cells retrieved from apical papillae (SCAP), dental pulp (DPSCs), human exfoliated deciduous teeth (SHED), wisdom teeth, and fibroblasts of the oral mucosa and periodontal ligament [80, 81]. iPSCs offer an endless supply of dental epithelial cells without the ethical concerns or immunorejection risks associated with embryonic stem cells. Research has demonstrated that iPSCs can produce potential epithelial progenitors when cultured on collagen-coated dishes with bone morphogenic protein (BMP)-4 and retinoic acid (RA). Additionally, iPSCs can be co-cultured with dental epithelial cell line SF2 or ERM cells to differentiate into enamel-producing ameloblasts [82, 83]. However, the original phenotype's epigenetic memory in iPSCs, which persists even after

reprogramming, limits their differentiation potential and poses a risk of tumor formation from undifferentiated cells in the target cells. Another drawback is the multiple differentiation steps required to guide iPSCs from an undifferentiated state to enamel-producing cells [80].

Ameloblast differentiation-inducing factors

T-box1 (Tbx1) is one of the Brachyury-related transcription factor family, and its modification or absence can result in DiGeorge syndrome, a genetic disorder affecting the development of organs such as the heart, face, parathyroid, and teeth. Tbx1 has been identified as a promoter of ameloblast differentiation, proliferation, and enamel formation [84]. In a mouse model, the removal of Tbx1 resulted in the lack of enamel and ameloblasts, reduced cell proliferation, decreased amelogenin expression, and varying degrees of hypomineralization and hypoplasticity [85, 86]. The expression of Tbx1 in dental epithelium is associated with fibroblast growth factor (FGF) expression, which is crucial for ameloblast specification, survival, and proliferation. Globoside, which is also prominently expressed during tooth development, has been shown to enhance ameloblast differentiation by boosting the expression of enamel matrix proteins, epiprofin, and regulating runt-related transcription factor 2 (Runx2) expression when administered exogenously in HAT-7 cells, although it does not affect cell proliferation. The AmeloD transcription factor plays a critical role in tooth morphogenesis by regulating E-cadherin expression and epithelial–mesenchymal interactions. In a mouse model, the deletion of AmeloD led to hypoplasia, the formation of smaller teeth, and impeded cell migration. The knockout of nuclear factor 1-C also resulted in structurally defective enamel and reduced ameloblast differentiation by regulating the osterix pathway [85, 87]. Additionally, TGF-β-1 can promote enamel mineralization and maturation by regulating the expression of RUNX2 and WD repeat-containing protein 72 (WDR72). It has also been shown that TGF-β-1, BMP-2-soaked apatite, and interleukin-7 (IL-7) can induce ameloblast differentiation. Basic fibroblast growth factor (FGF-2) also influences ameloblast differentiation and enamel matrix secretion [88]. However, there is a lack of time-controlled delivery of transcription and growth factors to guide stem cells differentiation into ameloblasts.

Tissue engineering and scaffold-based strategies

When dental epithelial SF2 cells are cultivated in three-dimensional spheroid cultures, their differentiation into ameloblasts and subsequent mineralization are enhanced. Consequently, using scaffold-based methods for enamel tissue regeneration appears to be a promising strategy [89, 90]. Scaffolds, crafted from both synthetic and natural biomaterials, have been developed in forms such as sponges, hydrogels, and meshes to aid in the regeneration of enamel or enamel-dental tissue complexes. These scaffolds offer structural support for dental tissue formation by providing cell-matrix signals and ideally are responsible for replicating the extracellular matrix (ECM), cellular interaction, proliferation, and differentiation. They should also degrade over time, possess suitable physical properties, and facilitate the diffusion process. Scaffold-based approaches may also allow for the integration of controlled delivery systems for the sustained release of signaling molecules and/or antibacterial agents in carious environments. Both polyglycolate/poly-L-lactate (PGA/PLLA) and poly(lactide-co-glycolide) (PLGA) scaffolds were shown to support tooth growth. Bioengineered teeth demonstrated the potential to replace missing teeth by implanting tissue-engineered constructs in place of the missing tooth. However, teeth grown in the fresh extraction site in the jaw were less organized compared to those grown in the omentum, indicating the need for further research to enhance the implantation process of bioengineered teeth in the jaw. A step-by-step cell-seeding technique has proven effective in promoting tooth regeneration and influencing the shape of tissue-engineered constructs. This method involves initially seeding mesenchymal cells densely onto collagen sponge scaffolds, followed by the addition of epithelial stem cells on top, ensuring direct contact between the two cell types. Additionally, fully formed heterotopic ossicles with structures resembling enamel, dentin, cementum, and bone, surrounded by cartilage tissue, as well as lipid-laden adipocytic clusters, were observed in co-transplants after 10 weeks [91, 92]. Scaffold-based methods also offer the potential to incorporate antibacterial molecules with active ingredients that trigger signaling pathways of cell repair and regeneration similar to those used for regeneration of dentine [88, 93].

Challenges and future perspectives

Despite the pressing demand for enamel regeneration and repair, the field of enamel tissue engineering remains in its early stages, facing numerous challenges and complexities. For example, the morphogenetic features of dental crown shapes differ significantly from those of regenerated enamel-dentin complexes, which tend to be either linear or circular with enamel situated within the dentin [94, 95]. Additionally, the arrangement of enamel prisms is somewhat irregular compared to natural enamel. The small size of regenerated crowns and lack of alignment with scaffold size represent another challenge that should be addressed [89, 96-98]. Furthermore, the intricate posttranslational protein processing required for crystal growth and the distinctive movement of ameloblasts, which shape HAp crystals into enamel rods, add further complexity to enamel tissue engineering [99, 100]. Consequently, more research is needed to understand how to regenerate enamel tissue with precise control over its shape and size.

Conclusion

Despite significant progress in developing techniques for enamel regeneration, numerous challenges remain. The

complex structure of enamel and its unique properties pose difficulties in replicating it through synthetic methods. Moreover, the success of current regeneration techniques often varies based on external factors and the conditions under which they are applied. Future research is likely to focus on refining the parameters for enamel regeneration, improving the integration and compatibility of artificial materials with natural enamel, and further exploring the use of stem cell therapy in dentistry. As this field advances, interdisciplinary collaboration among experts in materials science, cell biology, and clinical dentistry will be essential for creating better enamel regeneration strategies. Enamel regeneration methods are at the forefront of dental science, offering innovative ways to restore both the structural integrity and function of this vital tissue. By integrating biochemical methods, nature-inspired design, and advancements in tissue engineering, significant strides have been made in understanding and replicating the complex processes involved in enamel formation. As research continues to uncover new techniques and enhance existing ones, the potential for successful enamel regeneration is expected to increase, promising improved dental treatment options in the future.

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